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10/553,612	10/18/2005	Vladimir P. Torchilin	NU-604XX	1991

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EXAMINER	
SHEIKH, HUMERA N	
ART UNIT	PAPER NUMBER
1615	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,612	TORCHILIN ET AL.	
	Examiner	Art Unit	
	Humera N. Sheikh	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *17-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/18/05; 1/20/06; 5/21/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Receipt of the Response to Restriction Requirement and Applicant's Arguments/Remarks filed 06/29/09 and the Information Disclosure Statements (IDS) filed 10/18/05, 01/20/06 and 05/21/07 is acknowledged.

Applicant's election with traverse of Group II (claims 1, 9-19) in the reply filed on 29 June 2009 is acknowledged. The traversal is on the ground(s) that "the specified drug delivery system in Groups I and II is the same in each group; Group II being a preferred embodiment of Group I". This was found persuasive. Accordingly, the restriction requirement between Groups I and II has been withdrawn. The Restriction requirement has now been reformulated (see below), as was discussed in the telephonic conversation with the attorney of record (Holliday C. Heine) on 09 October 2009.

Claims 1-22 are pending in this action. Claims 17-22 have been withdrawn (non-elected invention). Claims 1-16 are rejected.

* * * * *

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 1-16, drawn to a drug delivery system.

Group II, claim(s) 17-22, drawn to a method of administering a targeted pharmaceutical agent.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The special technical feature that is lacking is the particular mode of administration (systemically or locally as in Group II versus Group I which can be oral administration).

During a telephone conversation with Holliday C. Heine on 09 October 2009 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-16. Affirmation of this election must be made by applicant in replying to this Office action. Claims 17-22 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

* * * * *

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2 and 4-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Alkan-Onyuksel *et al.* (hereinafter "Alkan-Onyuksel") (U.S. Pat. No. 6,322,810).

Alkan-Onyuksel ('810) discloses biologically active micelle products comprising biologically active amphipathic compounds in association with a micelle and methods of preparing the biologically active micelle products (see column 11, lines 33-36). According to the invention, polyethylene glycol (PEG) is covalently conjugated to distearoyl-phosphatidylethanolamine (DSPE) to form polymeric micelles which are then passively loaded with an amphipathic compound such as vasoactive intestinal peptide (VIP). The PEG-PE forms micelles with a hydrophobic core consisting of the diacyllipid – phosphatidylethanolamine (PE) fatty acid chains which is surrounded by a hydrophilic shell formed by the PEG polymer (col. 11, lines 49-55). The micelles offer improved stability and are useful in a various therapeutic, diagnostic and cosmetic applications (col. 14, lines 5-8). The invention provides improved diagnostic compositions comprising biologically active micelle products as discussed at col. 15, lines 18-33. These teachings read on instant claims 1-2, 6 and 7.

The method of preparation comprises the steps of a) mixing a combination of one or more lipids covalently bonded to a water-soluble polymer; b) forming sterically stabilized micelles from said combination of lipids and c) incubating micelles from step b) with a biologically active amphipathic compound under conditions whereby the compound becomes associated with said micelles from step b) in an active conformation (col. 11, lines 56-67). The biologically active amphipathic compound may also be co-precipitated with lipids to form micelles with incubation not required, the method comprising mixing one or more lipids covalently bonded to a water-soluble polymer with a biologically active amphipathic compound; forming sterically stabilized micelles from the mixture of step a) under conditions whereby the compound becomes associated with

said micelles in an active conformation (col. 12, lines 1-14). The water-soluble polymer is preferably PEG (col. 12, lines 15-25).

Suitable and preferred amphipathic compounds disclosed include VIP/growth hormone release factor (GRF), including biologically active analogs thereof (col. 12, lines 26-48). Preferred lipids disclosed include DSPE covalently bonded to PEG (PEG-DSPE) alone or in further combination with phosphatidylcholine (PC) and phosphatidylglycerol (PG) in further combination with cholesterol (Chol) and/or calmodulin (col. 13, line 65 - col. 14, line 4).

The micelles have an average diameter of less than about 20 nm (col. 12, lines 52-53). This teaching overlaps with and reads on the diameter of claim 8 (diameter in the range of 5 to 100 nm).

The PEG polymer is at a molecular weight between 1000 and 5000 (col. 13, lines 64-65). This teaching overlaps with and reads on the molecular weight recited in claims 4 and 5 (between 500-10,000 daltons and between 1,000 to 8,000 daltons, respectively).

The micellar formulations enhance bioactivity of the biologically active peptides, improve efficacy and demonstrate stability (col. 11, lines 36-40); (col. 14, lines 5-6).

The instant claims are anticipated by Alkan-Onyuksel.

* * * * *

Claims 1-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Unger *et al.* (hereinafter "Unger") (US Pub. No. 2002/0041898).

Unger ('898) discloses targeted delivery systems for bioactive agents comprising in combination with an effective amount of bioactive agent, a targeted matrix which comprises a polymer and a targeting ligand. The targeting ligand is covalently associated

with the polymer and the bioactive agent is associated non-covalently with the polymer, whereby the bioactive agent is homogeneously dispersed throughout the matrix (see p. 2, ¶ 0010-0013). The polymers employed may be linked or conjugated to a lipid, preferably a phospholipid, to provide a polymer-lipid conjugate (p. 8 ¶ 0071 & 0074). Preferred polymer-lipid conjugates are polymer-conjugated diacyllipids – such as phosphatidyl-ethanolamines (p. 9 ¶ 0075). In an embodiment, the composition comprises a matrix of a phospholipid conjugated to a linear hydrophilic polymer, such as dipalmitoylphosphatidylethanolamine (DPPE) linked to polyethylene glycol (PEG) (i.e., PEG 5000) (p. 2 ¶ 0016). These teachings read on instant claims 1, 6, 7, 9, 10, 13 and 14.

Preferred among the polymers is PEG in molecular weights ranging from about 400 to about 100,000 daltons (p. 7 ¶ 0064). This teaching overlaps with and reads on the molecular weight recited in claims 4, 5 and 12 (between 500-10,000 daltons and between 1,000 to 8,000 daltons, respectively).

With regards to the matrix, Unger states that the morphology of the matrix may be particulate where the particles are in the form of nanoparticulate structures or the morphology of the matrix may be micellar (p. 4 ¶ 0048). This teaching reads on the instant delivery system comprising a "micelle". The diameter of the particles ranges from about 1 nm to less than about 1000 nm (p. 5 ¶ 0050, p. 26 ¶ 0185). This teaching overlaps with and reads on the diameter of claim 8 (diameter in the range of 5 to 100 nm).

Targeting ligands disclosed include proteins, such as antibodies, peptides, polypeptides, cytokines, growth factors and fragments thereof, vitamins, polysaccharides,

steroids, hormones, cofactors, bioactive agents, genetic material and the like (p. 11 ¶ 0094-0095). These targeting ligands meet those of instant claim 15.

Bioactive agents disclosed include anti-neoplastic agents, anti-cancer agents, anti-inflammatory agents and the like (p. 23 ¶ 0141-0144). These classes of bioactive agents read on those of instant claim 2. Specific active agents disclosed include, for example, paclitaxel, camptothecin and tamoxifen (p. 24 ¶ 0153 & 0155). These bioactive agents read on those of instant claims 3 and 11.

Hence, Unger discloses delivery systems comprising a bioactive agent, a targeted matrix (micelles) comprised of a polymer – PEG and a targeting ligand. The composition comprises lipids such as phosphatidyl-ethanolamines, whereby the active agent is dispersed throughout the matrix. The system disclosed by Unger enables enhancement of the bioavailability of bioactive agents.

The instant claims are anticipated by Unger.

* * * * *

Claims 1-3, 6, 7, 9-11 and 13-15 are rejected under 35 U.S.C. 102(e) as being anticipated by Szoka, Jr. (hereinafter "Szoka") (U.S. Pat. No. 6,593,308).

Szoka ('308) discloses a drug delivery system for targeting tumor cells comprising a delivery vehicle having a low molecular weight targeting ligand - hyaluronan ligand having an affinity for CD44 receptors (col. 2, lines 39-41); (col. 3, lines 4-20). The hyaluronan modified lipid comprises a diacyllipid – phosphatidylethanolamine. Suitable delivery vehicles disclosed include micelles, in addition to liposomes, microspheres and the like (col. 2, lines 44-50); claim 15. Suitable

bioactive agents disclosed are anticancer agents or other therapeutic or diagnostic agents (col. 2, lines 50-53); (col. 3, lines 21-25). Exemplary lipids to which the hyaluronan ligand may be attached include phosphatidylethanolamine derivatives (col. 5, lines 25-37); claim 19. These exemplary lipids may further comprise amino-polyethylene glycols (col. 5, lines 37-38); (col. 14, line 43 – col. 15, line 23); claim 11. These teachings read on instant claims 1-2, 6, 7, 9, 10 and 13-15.

Suitable active agents disclosed include anti-cancer agents, such as paclitaxel, camptothecin and rhodamine (col. 5, lines 40-53); (col. 9, lines 60-61). These bioactive agents read on those of instant claims 3 and 11. Other classes of drugs include anti-inflammatory agents and the like (col. 5, lines 54-57). These classes of bioactive agents read on those of instant claim 2.

The instant claims are anticipated by Szoka.

* * * * *

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Unger *et al.* (hereinafter "Unger") (US Pub. No. 2002/0041898).

Unger ('898), as discussed above, teaches targeted delivery systems for bioactive agents comprising in combination with an effective amount of bioactive agent, a targeted matrix which comprises a polymer and a targeting ligand.

Unger does not teach the antibodies 2C5 or 2G4 of claim 16. However, Unger does teach targeting ligands composed generically of proteins, such as antibodies in addition to peptides, polypeptides, cytokines, growth factors and fragments thereof, vitamins, polysaccharides, steroids, hormones, cofactors, bioactive agents, genetic material and the like (p. 11 ¶ 0094-0095). Thus, the generic teaching of "antibodies" as suitable targeting ligand materials for use in the invention of Unger would necessarily encompass the species-specific antibodies - 2C5 or 2G4 of instant claim 16. As a result,

Unger meets the limitation of claim 16, based on their teaching of "antibodies" as suitable targeting ligand materials.

* * * * *

Claims 1-7 and 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Allen *et al.* (hereinafter "Allen") (U.S. Pat. No. 7,122,202).

Allen ('202) discloses a micellar suspension comprising a plurality of targeting conjugates for use in preparing a targeted, therapeutic liposome composition, each conjugated consisting essentially of a lipid, a polyethylene glycol (PEG) polymer and a targeting ligand having binding affinity for a receptor expressed on a cell attached to the distal end of the polymer (see columns 19-20, claim 1); (col. 2, lines 5-23); (col. 4, lines 58-63) and Abstract. The preferred hydrophilic polymer is PEG having a molecular weight ranging from about 500 to about 10,000 daltons (col. 2, lines 43-55); (col. 7, lines 61-67). This teaching exactly overlaps with and reads on the molecular weight recited in claims 4, 5 and 12 (between 500-10,000 daltons and between 1,000 to 8,000 daltons, respectively).

The lipid in the conjugates can be a diacyllipid, such as phosphatidylethanolamine (col. 3, lines 23-26); (col. 5, line 65 – col. 6, line 21, lines 39-44); claim 2.

Suitable active agents disclosed include cytotoxic agents, such as camptothecin (col. 3, lines 1-6). This bioactive agent reads on those of instant claims 3 and 11. Other classes of drugs include anti-neoplastic agents and anti-inflammatory agents (col. 8, lines 17-32). These classes of bioactive agents read on those of instant claim 2.

Targeting ligands disclosed include antibodies and antibody fragments, growth factors, vitamins, proteins, hormones and the like (col. 11 lines 1-53). These targeting ligands meet those of instant claim 15.

While Allen does not teach the antibodies 2C5 or 2G4 of claim 16, Allen teaches that antibodies and antibody fragments are preferred targeting ligands (col. 11, lines 40-53). Allen further teaches various antibodies/fragments thereof at Table 1 at column 11. Thus, the generic teaching of "antibodies" as suitable targeting ligand materials for use in the invention of Allen would necessarily encompass the species-specific antibodies - 2C5 or 2G4 of instant claim 16. As a result, Allen meets the limitation of claim 16, based on their teaching of "antibodies" as suitable targeting ligand materials. Furthermore, it would have been obvious to one of ordinary skill in the art to substitute one particular antibody targeting ligand with another based on the intended outcome and/or personal preference.

The instant invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made given the teachings of Allen. Allen explicitly teaches a micelle suspension for preparation of a liposome composition, whereby the composition is comprised of a lipid (i.e., phosphatidylethanolamine), a hydrophilic polymer (i.e., PEG) and a targeting ligand (i.e., antibody) attached to the distal end of the polymer in the composition. The composition comprises active agents (i.e., anti-neoplastic agents) such as those claimed. Thus, the teachings of Allen read on the drug delivery system claimed by Applicant.

* * * * *

Conclusion

--No claims are allowed at this time.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Humera N. Sheikh whose telephone number is (571) 272-0604. The examiner can normally be reached on Monday-Friday during regular business hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax, can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Humera N. Sheikh/
Primary Examiner, Art Unit 1615

hns

October 09, 2009